AMENDMENT IN SUPPORT OF RCE
Appln. No. 09/615,872

REMARKS

Reconsideration and further examination of this application is hereby requested. Claims 1-3, 5-6, 12-14 and 42-46 are currently pending in this application. Claims 4, 7-11 and 15-39 are cancelled. Claims 1-3, 5-6 and 12-14 are amended. Claims 42-46 are newly added in the application. No new matter has been added.

I. TELEPHONE INTERVIEW

A telephone interview was conducted between Examiner Grun and the undersigned on August 4, 2004 to discuss amending the claims to place them in condition for allowance. The Examiner reiterated comments found in the non-final and final office action wherein the Examiner stated that a deposit of biological material would overcome the §112 paragraph 1. Further, the Examiner stated that amending the claims directed to the antibody to recite the deposit would overcome the §103 obviousness rejection. In particular, proposed claims 42-44 were discussed and the Examiner determined that claims 42-43 would overcome all of the rejections made in the previous office actions if a deposit of biological material is made.

The applicant has made deposit of the biological material and amended the claims to recite ATCC No.PTA-6133 of the hybridoma deposit. Additionally, a true copy of the Certificate of Deposit is filed herewith.

Additionally, Applicant and Examiner discussed entering after final amendments with remarks for claims directed to generic antibodies that share the epitope specificity of the KKO antibody as produced by the hybridoma under deposit ATCC NO.: PTA-6133 as recited in claim 44. However, since claim 44 was not previously considered, the Examiner stated that the claims would represent new matter after final. The Examiner stated he would consider generic antibody claims of this scope in a request for continued examination and find them allowable if there were sufficient support for the claims in the application as filed.

Applicant in their request for continued examination has directed the Examiner to details within the specification supporting claims directed to antibodies which have the same or similar epitope specificity as the KKO monoclonal antibody epitope in an effort to facilitate the Examiner's examination of claims 44-46 drawn to antibodies having the same or similar epitope specificity as the KKO monoclonal antibody.

II. 35 U.S.C. §112, first paragraph

Claims 1-6, 12-14, 40 and 41 are rejected under 35 U.S.C. §112 first paragraph. The Examiner states that:

> "A suitable deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. §112, first paragraph, for claims directed to the KKO hybridoma or antibodies produced thereby."

AMENDMENT IN SUPPORT OF RCE
Appln. No. 09/615,872

Applicant has canceled claims 4, 40 and 41. Applicant has amended claims 1-3, and 5-6 directed to a composition comprising an antibody and claims 12-14 directed to a method for humanizing a monoclonal antibody. Applicant has deposited the KKO hybridoma cell line with the ATCC patent depository and has received the ATCC Deposit No.: PTA-6133 for the deposit. A copy of the certificate of deposit is filed herewith.

Amended claims 1-3, 5-6 are directed to a composition comprising a monoclonal antibody produced by the hybridoma cell line deposited as PT-1630. Amended claims 12-14 refer to method of humanizing a monoclonal antibody produced by a hybridoma cell line deposited as ATCC No.: PTA-6133 and antibodies that compete with the KKO monoclonal antibody for binding to PF4/heparin. Newly added claims 42-46 refer to the hybridoma cell line deposited as PTA-6133 producing the KKO monoclonal antibody. Therefore, the deposit of biological material under 37 CFR §§1.801-1.809 overcomes the 35 U.S.C. §112 first paragraph rejection, and places claims 1-3, 5-6, 12-14 and 42-46 in condition for allowance.

III. 35 U.S.C. §112 second paragraph

Claims 1-6, 12-14, 40 and 41 are rejected under 35 U.S.C. second paragraph. Claims 4, 40 and 41 have been cancelled. Claims 1, 3, 5, 6, 13, and 14 have been amended and delete the phrase "said binding...with either PF4 or heparin alone". Claims 2

and 12 have been amended and provide an antecedent to the same phrase thereby overcoming this rejection and placing claims 1-3, 5-6, 12-14 in condition for allowance.

IV. 35 U.S.C. §103(a)

Claims 1-6 and 40 are rejected under 35 U.S.C. §103(a) as being unpatentable over Amiral (U.S. Pat. No.: 5,466,582) in view of Blank et al. (Clin. Exp. Immunol. 108: 333, 1997) for reasons of record in the prior rejection of the similar subject matter of claims 1-6. Applicant cancels claims 4 and 40. Claims 1-3, 5-6, have been amended to include a recitation of the biological material deposited. Amended claims 1-3, 5-6 and new claims 42-46 are not obvious in view of Amiral in light of Blank for the following reasons.

A. THE EXAMINER HAS FAILED TO ESTABLISH A *PRIMA FACIE* CASE OF OBVIOUSNESS FOR CLAIMS 1-3, 5-6 AND 42-46.

In order for a patent claim to be obvious, the prior art must teach or suggest all the limitations of that claim. "In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness." In re Rijckaert, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993).

Claims 1-3, 5-6 and 42-46 include a reference to the hybridoma cell line deposited as PTA-6133 and monoclonal antibodies generated there from. Additionally, the monoclonal

antibody produced from the hybridoma cell line deposited as PTA-1633 is also defined in terms of its binding specificity with PF4/heparin and epitope specificity for the PF4/heparin complex. See Page 51, line 8 through page 52, line 19.

Neither Blank nor Amiral alone or in combination teach, suggest or provide motivation to one of ordinary skill in the art the composition as described in claims 1-3, 5-6, nor the antibodies produced by the hybridoma cell line deposited under ATCC No. PTA-1633 as described in claims 42-46.

B. THERE IS NO MOTIVATION, SUGGESTION, OR TEACHING OF THE DESIRABILITY OF MAKING THE SPECIFIC COMBINATION THAT WAS MADE BY THE APPLICANT

Identification in the prior art of each individual part claimed in a patent is insufficient to defeat patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant. In an obviousness determination, the factual question of motivation to combine prior art is material to patentability, and cannot be resolved on subjective belief and unknown authority. In re Lee 1277 F.3d 1338, 1345, 61 U.S.P.Q.2d 1430, 1433-1434 (Fed. Cir. 2002). An Examiner can satisfy the

burden of showing obviousness of the combination only by showing some objective teaching in the prior art. Id. at 1344, 61 U.S.P.Q.2d at 1433-1434 ("The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record.").

Amiral teaches the use of secondary antibodies to detect primary antibodies (auto-antibodies) in a patient's plasma wherein the primary antibodies recognize the PF4/heparin complex. Amiral teaches the use of secondary antibodies to recognize the primary antibody produced by a patient in response to the PF4/heparin complex thereby making the primary antibody a necessary and essential part of the primary antibody/secondary antibody antigenic complex. Amiral does not teach, suggest nor contemplate the generation of primary antibodies to directly recognize the PF4/heparin complex. Further Amiral teaches away from generating a primary antibody (monoclonal or polyclonal) that directly recognizes the PF4/heparin complex as the purpose of the invention as described in Amiral is to determine whether a patient has generated auto-antibodies or primary antibodies to PF4/heparin complex as a marker for patients at risk for developing Thrombocytopenia upon heparin treatment.

Blank teaches the production of a mouse model of heparin induced thrombocytopenia wherein auto-antibodies produced in a mouse recognize mouse PF4/heparin complex. The mouse polyclonal

auto-antibodies are induced by administrating to a naïve mouse, affinity purified IgG containing anti-PF4/heparin antibodies from patients with heparin induced thrombocytopenia. The polyclonal mouse auto-antibodies induce heparin induced thrombocytopenia upon heparin challenge. Therefore the combination of Amiral in light of Blank does not and could not render claims 1-3, 5-6 and 42-46 obvious.

Further, the domains that are involved in epitope binding (the first and second domains but not the third domain of PF4 comprised the KKO epitope) were identified by the Applicant through competition binding studies with wild type human platelet factor 4 (hPF4) complexed to heparin and mutated hPF4 complexed to heparin. Claims 44-46 recite limitations dealing with epitope specificity of monoclonal antibodies that bind to the KKO epitope on the PF4/heparin complex.

Claims 44-46 are supported by the specification at page 51-52. Particularly, KKO antibodies share epitope specificity for the KKO epitope site on the hPF4 protein with HIT/HITT (3^{rd} domain insensitive) antibodies. The HIT/HITT (3^{rd} domain insensitive) antibodies show biding affinities to the hPF4 protein that are unaffected by serial mutations within the 3^{rd} domain of the hPF4 protein when complexed to heparin. See page 51, line 17 through page 52, line9.

Further epitope cross mapping between HIT/HITT (3^{rd} domain

insensitive) antibodies is illustrated through KKO monoclonal antibodies binding characterization to PF4 3rd domain mutants. KKO monoclonal antibody binding affinities are unaffected by hPF4 3rd domain mutants when complexed to heparin further demonstrating that this domain is not an epitope to which the KKO monoclonal binds. See page 52, lines 10-16 and FIG 5A.

The KKO epitope maps to nonconserved sequences as defined by the binding affinities of KKO and HIT/HITT (3rd domain insensitive) antibodies for mouse PF4 when complexed to heparin. Human PF4 and mouse PF4 share 80% amino acid sequence homology. The least conserved region is second domain of the protein. Neither KKO nor HIT/HITT (3rd domain insensitive) Abs bind to mouse PF4 further mapping the epitope to the first and second domains of hPF4. See page 51, line 31 through page 52, line 9. Neither Amiral nor Blank singly or in combination, contemplate the epitope specificity of antibodies which bind to the PF4/heparin complex. Therefore, claims 44-46 are non-obvious in view of Amiral in light of Blank and are in condition for allowance.

V. CLOSING

In view of the above, Applicant respectfully submits that independent claims 1, 12, 42, 43, 44, and 46 are patentable over the prior art. Applicant further submits that dependent claims 2-3, 5-6, 13-14, and 45 are patentable, at least as being

dependent from patentable independent claims, and are further patentable due to the additional limitations recited therein.

For the above reasons, Applicant respectfully submits that the application is in condition for allowance with claims 1-3, 5-6, 12-14 and 42-46. If there remain any issues that may be disposed of via a telephonic interview, the Examiner is kindly invited to contact the undersigned at the exchange given below.

The Director of the Patent and Trademark Office is authorized to charge any necessary fees, and conversely, deposit any credit balance, to Deposit Account No. 18-1579.

Respectfully submitted,
ROBERTS ABOKHAIR & MARDULA, LLC

Janeen Vilven

Janeen VILVEN
Reg. No. 47156
(505) 922-1400